Take-home messages

- Infection associated haemophagocytic syndrome (IAHS) is an uncommon disorder usually occuring in immunocompromised patients, consisting of a systemic reactive proliferation of erythrophagocytic histiocytes.
- IAHS most be considered a diagnostic possibility in the setting of recurrent AML/MDS or previous haematologic neoplasm.
- IAHS arises abruptly and serial examination of bone marrow in rapidly declining patients may facilitate occurate diagnosis and further study.

IAHS may be underdiagnosed because of its association with a variety of other serious diseases. The onset of IAHS is manifested by an abrupt change in clinical course characterised by high fever, severe constitutional symptoms, organomegaly and pancytopenia. Hepatosplenomegaly is usually present and lymphadenopathy, rash and diffuse pulmonary infiltrates are common. Often, there is a history of a recent viral-like illness. Many patients with IAHS have a fulminant clinical course. The mortality is 30–40% during the acute illness. Patients surviving the acute manifestations usually recover in 1–8 weeks.[1]

Haemophagocytic syndrome can arise from several immunocompromised clinical states and must be considered to be a diagnostic possibility in the setting of recurrent AML/MDS.[2–6] The bone marrow biopsy 17 days before death did not show haemophagocytosis, but postmortem examination of the bone marrow showed extensive erythrophagocytosis. This case highlights the need for serial examination of the bone marrow, especially in rapidly declining patients. IAHS has been associated with a variety of haematological malignancies, including AML, in the literature.[2] It is important to note that IAHS can be a rare but possible aggressive complication in the clinical course of patients with acute leukaemia. IAHS treated with the antineoplastic agent etoposide has resulted in the development of treatment-related AML and MDS.[7–9] This case further shows the association between IAHS and recurrent AML/MDS. Further studies should evaluate the cytogenetic changes in IAHS and how they relate to the cytogenetic changes in AML and other haematological malignancies. These studies may help to elucidate the relationship between haematological malignancies and IAHS.

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Competing interests: None.

Informed consent has been received for the publication of this article.

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Accepted 25 July 2005

REFERENCES

1 **Brunning RD**, McKenna RW. *Atlas of tumor pathology: tumors of the bone marrow*. Washington, DC: Armed Forces Institute of Pathology, 1993.
2 **Majluf-Cruz A**, Sosa-Camas R, Perez-Ramirez O, *et al*. Hemophagocytic syndrome associated with hematological neoplasias. *Leuk Res* 1998;**22**:893–8.
3 **Bertozzi AI**, Suc A, Rubie H, *et al*. Hemophagocytic syndrome associated with neutropenia after chemotherapy. *Arch Pediatr* 2002;**9**:125–9.
4 **Kumar M**, Boggino H, Hudnall SD, *et al*. Acute myeloid leukemia associated with hemophagocytic syndrome and t(4;7)(q21;q36). *Cancer Genet Cytogenet* 2000;**122**:26–9.
5 **Demirkan F**, Vural F, Ozsan GH, *et al*. Hemophagocytic syndrome associated with inappropriate secretion of antidiuretic hormone in lymphoma and acute myeloblastic leukemia: report of two cases. *Leuk Lymphoma* 2001;**42**:1401–4.
6 **Potter MN**, Foot AB, Oakhill A. Influenza A and the virus associated haemophagocytic syndrome: cluster of three cases in children with acute leukaemia. *J Clin Pathol* 1991;**44**:297–9.
7 **Takahashi T**, Yagasaki F, Endo K, *et al*. Therapy-related AML after successful chemotherapy with low dose etoposide for virus-associated hemophagocytic syndrome. *Int J Hematol* 1998;**68**:333–6.
8 **Stine KC**, Saylors RL, Sawyer JR, *et al*. Secondary acute myelogenous leukemia following safe exposure to etoposide. *J Clin Oncol* 1997;**15**:1583–6.
9 **Imashuku S**, Teramura T, Kuriyama K, *et al*. Risk of etoposide-related acute myeloid leukemia in the treatment of Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis. *Int J Hematol* 2002;**75**:174–7.

Kikuchi's disease displaying a t(2:16) chromosomal translocation

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J Clin Pathol 2007;**60**:433–435. doi: 10.1136/jcp.2006.038646

Kikuchi's disease is a rare self-limiting lymphoproliferative condition of unknown aetiology, characterised by acute or subacute necrotising lymphadenitis. It is a benign condition that can mimic malignant lymphoma. In this report, a case of Kikuchi's disease associated with a chromosomal abnormality is described. This is the first report in the literature of such a case and it highlights an important learning point; benign lymphoproliferative conditions can be associated with chromosomal abnormalities that are more typically associated with malignant lymphoproliferative conditions such as malignant lymphoma. The report illustrates the necessity for interpreting cytogenetic data in the relevant clinical and histopathological context in a multidisciplinary setting to avoid misdiagnosis and inappropriate treatment.

Kikuchi's disease (KD) is a rare, benign, self-limiting lymphoproliferative condition of unknown aetiology, characterised by acute or subacute necrotising lymphadenitis. It was first described in 1972 by Kikuchi[1] and Fujimoto,[2] and is synonymous with Kikuchi–Fujimoto disease, Kikuchi's necrotising lymphadenitis, Kikuchi's syndrome and necrotising lymphadenopathy without granulocytic infiltrations. The disease primarily affects the cervical lymph nodes in young women (female:male sex ratio is 3:1, with a mean age of around 30 years), and in approximately 50% of cases, the patient experiences a fever and a flu-like illness. Extranodal manifestations such as cutaneous erruptions, hepatosplenomegaly and neurological

Abbreviation: KD, Kikuchi's disease.

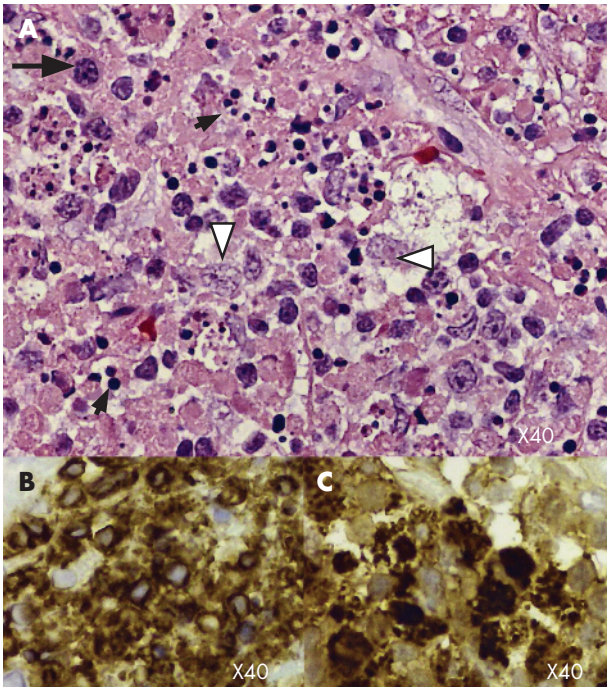

Figure 1 H&E-stained lymph node biopsy (A) showing aggregates of lymphoid cells with central karyorrhectic and apoptotic debris (small arrows) surrounded by a mixed population of histiocytes (arrowheads) and immunoblast-like cells (large arrow). (B) Immunohistochemical examination showing the immunoblasts to be of T lineage (CD3 positive). (C) Histiocytes in the abnormal paracortical foci were strongly positive for myeloperoxidase.

involvement are rare. The disease process is self-limiting, full resolution is usually seen within 2–3 months of diagnosis and relapses are rare.[3–5] In this paper, we present what we believe to be the first reported case of KD associated with a cytogenetic abnormality, illustrating the importance of interpreting cytogenetic data from lymph node biopsies in the relevant clinical and histopathological context to avoid misdiagnosis.

CASE REPORT

A 20-year-old woman presented with painless axillary lymphadenopathy, weight loss and anorexia. On examination, she seemed clinically well, but had two firm, mobile, non-tender lumps measuring 1.0 cm in the roof of her right axilla. No breast masses or evidence of infection in areas drained by the axillary nodes were detected. Supraclavicular/cervical lymphadenopathy and extranodal involvement were absent. Blood biochemistry and haematology were within the normal range. Fine-needle aspiration cytology showed only reactive lymphoid hyperplasia. A review at 5 weeks detected an increase in the lymphadenopathy and a lymph node biopsy was carried out.

Pathological findings

Histological examination showed a largely intact architecture with reactive lymphoid follicles in the cortical areas. Expansion of paracortical foci by large irregular aggregates of lymphoid cells was noted. Centrally, the aggregates contained abundant karyorrhectic and apoptotic debris with foci of frank necrosis surrounded by a mixed population of histiocytes, immunoblast-like cells and plasmacytoid monocytes (fig 1A).

Immunohistochemical examination showed the immunoblast-like cells to be of T lineage (CD3 positive; fig 1B) with expression of pan-T cell antigens CD2, CD5 and CD7. Expression of CD8 was greater than that of CD4. Expression of CD30, CD56, EMA and

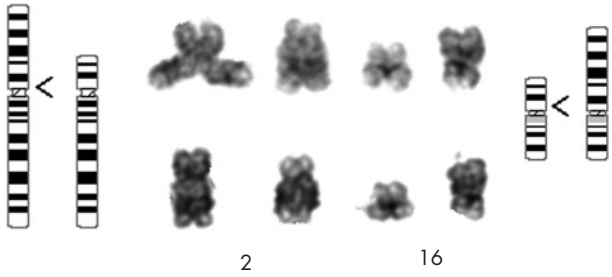

Figure 2 G-band partial karyotypes from fresh lymph node tissue showing t(2;16) (p11.2;p11.2). Abnormal chromosome on the right of each pair, arrowheads indicate position of breakpoints.

ALK1 was absent. Epstein–Barr virus immunohistochemistry and in situ hybridisation for Epstein–Barr virus-encoded RNA were negative. Histiocytes in the abnormal paracortical foci expressed CD68, MAC387 and were strongly positive for myeloperoxidase (fig 1C). Polymerase chain reaction performed on DNA extracted from a sample of fresh nodal tissue showed polyclonal patterns of immunoglobulin heavy chain and T cell receptor γ gene rearrangement. Conventional cytogenetic analysis was performed on G-banded preparations of cells mechanically disaggregated from the same fresh tissue. The resulting cell suspension was cultured overnight in the presence of colcemid (0.06 μg/ml) before harvesting by routine laboratory methods (30 min exposure to 0.075 M potassium chloride followed by fixation in 3:1 methanol:acetic acid). G-banded preparations were analysed according to the International System of Cytogenetic Nomenclature (1995). The following abnormal karyotype was observed: 46,XX, t(2;16) (p11.2;p11.2)[5]/46, XX[15] (fig 2). This was the sole abnormality detected. Subsequent cytogenetic analysis of a peripheral blood sample from the patient showed a normal female karyotype, ruling out the possibility of a constitutional abnormality.

On the basis of the histological and immunohistochemical findings alone, we were confident of the diagnosis of KD. However, the presence of a cytogenetic abnormality led us to seek a second opinion from an expert in the field, Dr John KC Chan, Queen Elizabeth Hospital, Hong Kong, who concurred with our diagnosis.

Follow-up information

The patient received no specific treatment. The lymphadenopathy resolved spontaneously and she remains well 4 years after her initial presentation.

DISCUSSION

Histologically, Kikuchi's lymphadenitis is characterised by infiltration of the cortex or paracortex by numerous proliferating crescentic histiocytes, T immunoblasts, small lymphocytes and plasmacytoid monocytes, associated with total or partial

Take-home messages

- Kikuchi's disease is a benign, self-limiting lymphoproliferative condition that can mimic malignant lymphoma
- Kikuchi's disease can be associated with chromosomal abnormalities that are more typically associated with malignant lymphoma
- Interpretation of cytogenetic data must occur in the relevant clinical and histopathological context in a multidisciplinary setting to avoid misdiagnosis and inappropriate treatment

necrosis of the affected node.[4 5] The differential diagnosis is wide and varied, including systemic lupus erythematosus-associated lymphadenopathy, herpes simplex-associated lymphadenopathy, non-Hodgkin's lymphoma, plasmacytoid T cell leukaemia, Kawasaki disease, nodal colonisation by acute myeloid leukaemia and infectious lymphadenitis.[4 5]

One of the most frequently reported misdiagnoses is that of malignant lymphoma.[6] Pathological features that help in discriminating Kikuchi's lymphadenitis from lymphoma include the partial maintenance of lymph node architecture, the presence of small and large atypical lymphocytes, phagocytic histiocytes, extracellular debris and the absence of plasma cells, multinucleated giant cells and Reed–Sternberg cells.[4–6] Myeloperoxidase expression in the histiocytic component of the infiltrate is also said to favour a diagnosis of KD.[7] Conversely, chromosomal aberrations, particularly translocations, are often observed in malignant lymphoma but, to the best of our knowledge, have not been previously reported in Kikuchi's disease. Nevertheless, despite finding a t(2;16) in our case, we remain convinced that it represents a bona fide example of Kikuchi's disease in view of the typical pathological findings, the spontaneous resolution of symptoms and the fact that the patient remains free from disease 4 years after diagnosis. Moreover, although the presence of a cytogenetic aberration may be used to support the diagnosis of lymphoma, it should not be used as the sole determinant of malignancy as clonal cytogenetic abnormalities may also occur in reactive lymphoid hyperplasias.[8]

The aetiology of KD remains unknown, although infective and/or autoimmune causes have been postulated.[4 5] The current case raises the additional intriguing possibility that some examples may be associated with a chromosomal translocation, and the lack of previous similar reports in the literature may simply reflect the fact that KD is a relatively rare condition, and that cytogenetic analysis is not routinely performed on lymph node biopsies in most laboratories. It is possible that the cytogenetic abnormality identified here is coincidental and not linked to the pathogenesis of the disease, perhaps occurring as a secondary phenomenon in rapidly proliferating cells within the necrotic foci. Alternatively, the chromosomal translocation may be linked to the pathogenesis of the disease. A search of the Mitleman database (http://cgap.nci.nih.gov/Chromosomes/Mitelman) shows only rare reports of balanced translocations involving the 2p11 and/or 16p11 loci, predominantly in cases of acute lymphoblastic leukaemia/lymphoma, incuding three cases with a t(2;16)(p11;p11), as well as occasional cases of B cell non-Hodgkin's lymphoma and myeloid leukaemia, suggesting a role in the development of haematological neoplasms.[9 10] Candidate genes at these loci include the immunoglobulin κ joining region, immunoglobulin κ variable region, granulysin (T lymphocyte activation gene 519) and latent transforming growth factor β binding protein 1 on chromosome 2p, and integrin α-D, integrin α-L, B cell chronic lymphocytic leukaemia/lymphoma 7C and interleukin 21 receptor on chromosome 16p. However, there are no reports of these genes being associated with KD, and further studies will be required to ascertain their significance in this disease.

In summary, this case report illustrates that Kikuchi's lymphadenitis can be associated with chromosomal abnormalities and great care should be taken when diagnosing malignant lymphoma on the basis of cytogenetics when the lymph node morphology and clinical features might also suggest Kikuchi's disease.

ACKNOWLEDGEMENTS

We thank Dr John KC Chan, Queen Elizabeth Hospital, Kowloon, Hong Kong, for reviewing the case. Dr Goodlad holds a part time Senior Clinical Research Fellowship in the Division of Pathology and Neuroscience, University of Dundee, funded by the Leng Charitable Trust at the Ninewells Cancer Campaign, Dundee, UK.

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Accepted 29 August 2006

REFERENCES

1 **Kikuchi M**. Lymphadenitis showing focal reticulum cell hyperplasia with nuclear debris and phagocytosis. Acta haematologica Japonica. *Nippon Ketsueki Gakkai Zasshi* 1972;**35**:379–80.
2 **Fujimoto Y**, Kozima Y, Yamaguchi K. Cervical subacute necrotizing lymphadenitis: a new clinicopathologic entity. *Naika* 1972;**20**:920–7.
3 **Kim KJ**, Jee MS, Chang SE, Choi JH, *et al*. Kikuchi-Fujimoto disease with papulopustular skin manifestations. *Clin Experiment Dermatol* 2003;**28**:142–4.
4 **Bosch X**, Guilabert A, Miquel R, *et al*. Enigmatic Kikuchi-Fujimoto disease. *Am J Clin Pathol* 2004;**122**:141–52.
5 **Onciu M**, Medeiros LJ. Kikuchi-Fujimoto lymphadenitis. *Adv Anatomic Pathol* 2003;**10**:204–11.
6 **Menasce LP**, Banerjee SS, Edmondson D, *et al*. Histiocytic necrotizing lymphadenitis (Kikuchi-Fujimoto disease): continuing diagnostic difficulties. *Histopathology* 1998;**33**:248–54.
7 **Pileri SA**, Facchetti F, Ascani S, *et al*. Myeloperoxidase expression by histiocytes in Kikuchi's and Kikuchi-like lymphadenopathy. *Am J Pathol* 2001;**159**:915–24.
8 **Grace J**, Hall BE, Lew M, *et al*. Cytogenetic abnormalities in benign lymphoid hyperplasia: a dual-parameter study using chromosome analysis and flow cytometry. *Int J Cancer* 1989;**44**:959–64.
9 **Heerema NA**, Palmer CG, Weetman R, *et al*. Cytogenetic analysis in relapsed childhood acute lymphoblastic leukaemi. *Leukaemia* 1992;**6**:185–92.
10 **Lowe LR**, Heerema NA, Cheerva AC, *et al*. A new nonrandom chromosomal abnormality, t(2;16)(p11.2;p11.2), possibly associated with poor outcome in childhood acute lymphoblastic leukemia. *Cancer Genet Cytogenet* 1992;**64**:60–4.